P930027

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

DCS Copy

Memorandum

Date SEP 15 1995

From Director, Office of Device Evaluation (HFZ-400)
Center for Devices and Radiological Health (CDRH)

Subject Premarket Approval of Diagnostic Products Corporation's Coat-A-Count® PSA IRMA - Action

To The Director, CDRH, ORA _____

ISSUE. Publication of a notice announcing approval of the subject PMA.

FACTS. Tab A contains a FEDERAL REGISTER notice announcing:

(1) a premarket approval order for the above referenced medical device (Tab B); and

(2) the availability of a summary of safety and effectiveness data for the device (Tab C).

RECOMMENDATION. I recommend that the notice be signed and published.

Susan Alpert, Ph.D., M.D.

Attachments
Tab A - Notice
Tab B - Order
Tab C - S & E Summary

DECISION

Approved _____ Disapproved _____ Date _____

Prepared by E. Radha, Ph.D., CDRH, HFZ-440, 9/11/95, 594-1293

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

[DOCKET NO.]

Diagnostic Products Corporation.; Premarket Approval of Coat-A-Count® PSA IRMA

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing its approval of the application by Diagnostic Products Corporation, Los Angeles, CA, for premarket approval, under section 515 of the Federal Food, Drug, and Cosmetic Act (the act), of Coat-A-Count® PSA IRMA. FDA's Center for Devices an Radiological Health (CDRH) notified the applicant, by letter on SEP 15 1995, of the approval of the application.

DATE: Petitions for administrative review by (insert date days after date of publication in the FEDERAL REGISTER).

ADDRESS: Written requests for copies of the summary of safety and effectiveness data, and petitions for administrative review to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 1-23, 12420 Parklawn Drive, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Peter E. Maxim, Ph.D.

Center for Devices and Radiological Health (HFZ -440)

Food and Drug Administration

2098 Gaither Road

Rockville, MD 20850

301-594-1294

SUPPLEMENTARY INFORMATION: On August 10, 1993, Diagnostic Products Corporation, Los Angeles, CA 90045, submitted to CDRH an application for premarket approval of Coat-A-Count® PSA IRMA. The device is an immunoradiometric assay intended for the quantitative measurement of prostate-specific antigen (PSA) in serum to aid in the management of prostate cancer patients. In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Immunology Devices Panel, an FDA advisory panel, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

On SEP 15, 1995, CDRH approved the application by a letter to the applicant from the Director of the Office of Device Evaluation, CDRH.

A summary of the safety and effectiveness data on which CDRH based its approval is on file in the Dockets Management Branch (address above) and is available from that office upon written request. Requests should be identified with the name of the device and the docket number found in brackets in the heading of this document.

OPPORTUNITY FOR ADMINISTRATIVE REVIEW

Section 515(d)(3) of the act (21 U.S.C. 360e(d)(3)) authorizes any interested person to petition, under section 515(g) of the act (21 U.S.C. 360e(g)), for administrative review of CDRH's decision to approve this application. A petitioner may request either a formal hearing under part 12 (21 CFR part 12) of FDA's administrative practices and regulations or a review of the application and CDRH's action by an independent advisory committee of experts. A petition is to be in the form of a petition for reconsideration under 10.33(b) (21 CFR 10.33(b)). A petitioner shall identify the form of review requested (hearing or independent advisory committee) and shall submit with the petition supporting data and information showing that there is

a genuine and substantial issue of material fact for resolution through administrative review. After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issue to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

Petitioners may, at any time on or before (insert date 30 days after date of publication in the FEDERAL REGISTER), file with the Dockets Management Branch (address above) two copies of each petition and supporting data and information, identified with the name of the device and the docket number found in brackets in the heading of this document. Received petitions may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 515(d), 520(h), and (21 U.S.C. 360e(d), 360j(h)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10) and redelegated to the Director, Center for Devices and Radiological Health (21 CFR 5.53).

Dated:_____.

_____

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

Edward M. Levine, Ph.D.
Manager, Clinical Affairs
Diagnostic Products Corporation
5700 West 96th Street
Los Angeles, California 90045

SEP 15 1995

Re: P930027
Coat-A-Count® PSA IRMA
Filed: August 10, 1993
Amended: January 21, 1994; April 8, 1994; August 3, 5, and 19, 1994; and September 11, 1995

Dear Dr. Levine:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the Coat-A-Count® PSA IRMA. This device is an immunoradiometric assay indicated for the quantitative measurement of prostate-specific antigen (PSA) in serum to aid in the management of prostate cancer patients. We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution and use of this device are restricted to prescription use in accordance with 21 CFR 801.109.

Expiration dating for this device has been established and approved at 60 days, stored at 2°C - 8°C. This is to advise you that the protocol you used to establish this expiration dating is considered an approved protocol for the purpose of extending the expiration dating as approved by 21 CFR 814.39 (a)(8).

CDRH will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. Within 30 days of publication of the notice of approval in the FEDERAL REGISTER, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that as soon as possible, and before commercial distribution of your device, that you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Peter Maxim, Ph.D. at (301) 594-1293

Sincerely yours,

Susan Alpert, Ph.D., M.D.
Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

Summary of Safety and Effectiveness Data

Coat-A-Count® PSA IRMA

P930027

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Immunoradiometric test system for the quantitative measurement of prostate specific antigen (PSA) in human serum.

Device Trade Name: Coat-A-Count® PSA IRMA

Applicant's Name and Address: Diagnostic Products Corporation (DPC)
5700 West 96th Street
Los Angeles, California 90045

Premarket Approval Application (PMA) Number: P930027

Panel Recommendations: Pursuant to section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not the subject of an FDA Immunology Devices Advisory Panel meeting because the information in the PMA substantially duplicates information previously reviewed by this panel.

II. INDICATIONS FOR USE

Coat-A-Count® PSA IRMA is an immunoradiometric assay intended for the quantitative measurement of prostate-specific antigen (PSA) in serum to aid in the management of prostate cancer patients.

Background

Prostate specific antigen (PSA), first identified and characterized by Wang et. al, in 1979, is a glycoprotein monomer with protease activity.[1 2] PSA has an isoelectric point of approximately 6.9 and a molecular weight of approximately 33-34 kilodaltons, and contains approximately 10 percent carbohydrate. [1 2]

Amino acid sequencing [3 4] has been reported and the gene for PSA has been cloned.[4] PSA is biochemically and immunologically distinct from Prostatic Acid Phosphatase (PAP) and does not exhibit enzymatic phosphatase activity.[5] PSA is localized in the cytoplasm of prostatic ductal epithelium and in secretions of the ductal lumina.[6] Because PSA is a secretory protein of the prostate, it can be recovered and purified both from prostatic tissue and from seminal plasma.[7] PSA has been found to be exclusively associated with prostate tissue and elevated serum PSA has

been found in patients with prostate cancer, benign prostatic hypertrophy (BPH) or hyperplasia, and inflammatory conditions of other adjacent genitourinary tissues, but not in healthy men, men with nonprostatic carcinoma, healthy women or women with cancer.[5-8]

Serum PSA as measured with this device is not suitable as a screen for prostate cancer because elevated PSA concentrations are also observed in patients with BPH,[8] nor is it recommended as a guide in disease staging.

PSA determinations can be useful in detecting metastatic or persistent disease in patients following surgical or medical treatment of prostate cancer.[9,10] Persistent elevation of PSA following treatment or an increase in the pretreatment PSA concentration is indicative of recurrent or residual disease.[11-15] Therefore, PSA is accepted as an aid in the management of prostate cancer patients.[11-15] Concurrent measurement of PAP may contribute additional information.[16]

III. DEVICE DESCRIPTION

Diagnostic Products Corporation (DPC) Coat-A-Count® PSA IRMA herein referred to as the DPC PSA IRMA is an in vitro diagnostic medical device designed for the quantitative measurement of PSA in serum.

The patient sample or PSA calibrators and PSA Assay Buffer (PSAB) are added to PSA Antibody-Coated Tubes. PSA becomes bound to the surface of the tube. Iodine-125 labeled anti-PSA murine monoclonal antibody is added and PSA bound to the tube becomes labeled.

Unbound iodine-125 labeled anti-PSA is removed by washing. The tube is then placed in a gamma counter and the results are computed as percent of maximal binding. The PSA concentration is directly proportional to the radioactivity present in the tube. The concentration of PSA in the patient sample is obtained by interpolation from the calibration curve. The DPC PSA IRMA assay is calibrated to measure between 0 and 150 nanograms (ng) of PSA per milliliter (mL) of serum.

IV. ALTERNATIVE PRACTICES AND PROCEDURES

The DPC PSA IRMA is used in conjunction with routine medical practices and procedures in the management of prostate cancer patients. The following are alternative practices and procedures:

1) Serial determinations of prostatic acid phosphatase
2) Serial determinations of bone alkaline phosphatase

3) Serial determinations of total acid phosphatase
4) Serial determinations of total alkaline phosphatase
5) Bone scans
6) Whole body scans
7) Lymphangiography, lymphadenectomy, and biopsies
8) Ultrasonic and digital rectal examinations
9) Determination of PSA level/s with other legally marketed tests

V. MARKETING HISTORY

DPC PSA IRMA has been marketed in the following countries: Aubu Dhabi, Argentina, Boliva, Canada, PuertoRico, Haiti, Dominion Republic, Chile, Colombia, Costa Rica, Denmark, Greece, Gautemala, Netherlands, India, Italy, Jordan, Kuwait, Lebanon, Mexico, Panama, People's Republic of China, Peru, Philipines, Portugal, Saudi Arabia, Switzerland, Syria, Taiwan, Thailand, and Uruguay.

DPC PSA IRMA has not been withdrawn from the market in any country for any reason related to the safety and effectiveness of the device.

VI. Potential Adverse Effects of Device on Health

When the present device is used as indicated, and the results are evaluated in conjunction with all available clinical information, there are no known potential adverse effects to the health of patients undergoing management for cancer. False test results, though, could affect the physician's decisions regarding patient treatment. If falsely low, the physician may delay providing beneficial treatment in cases of recurring or progressive cancer. If falsely elevated, medical decisions may be made that result in needless therapy or change in treatment, including unnecessary surgical or radiation procedures.

Precautions

The DPC PSA IRMA assay is not approved as a screening test or to be used as a sole diagnostic tool. PSA levels should not be used as absolute evidence of presence or absence of malignant disease.

The concentrations of PSA in a given specimen determined with different assays can vary due to differences in assay methods and reagent specificity. The results reported by the laboratory to the physician must include the identity of the assay used. Values obtained with PSA assays from different manufacturers cannot be used interchangeably. Before changing assays, the laboratory must confirm baseline values for patients being serially monitored.

Since elevated levels of PSA have been reported in some patients with non-malignant diseases of the prostate, such as BPH, this device alone should not be used to screen for or diagnose prostate cancer.

Warnings

PSA expression may be altered due to hormonal therapy for prostate cancer. Consequently, a low PSA result following a prostatic cancer treatment which includes hormonal therapy may not adequately reflect the presence of residual or recurrent disease.[17]

Specimens from patients who have received preparations of mouse monoclonal antibodies for diagnosis or therapy may contain human anti-mouse antibodies (HAMA) and may result in erroneous results.

Manipulations of the prostate (e.g. biopsy, transurethral resection and prostatectomy) can lead to transient and even high increases in circulating PSA.[18] Studies on whether digital rectal examination affects PSA levels have had conflicting results.[19] [20] Blood samples should be obtained prior to any manipulation of the prostate whenever possible. If this is not possible, it is important to note the exact time of sampling for PSA analysis in relation to any prior manipulation of the prostate. PSA has an estimated circulating half-life of 2.2 days. Serum samples should be obtained approximately 3 weeks after manipulation of the prostate to avoid any effect on the PSA level due to manipulation.

A single PSA value should not be the basis for decisions regarding patient care. Repeat determinations utilizing serially drawn specimens are recommended.

The PSA normal range is not applicable when managing patients who have been treated or are currently receiving treatment for their disease. In patients who have undergone surgery for complete removal of the prostate, the presence of any detectable PSA indicates the possible presence of residual prostate tissue, possibly of a cancerous nature, and should be investigated.[12]

VII. SUMMARY OF STUDIES

Preclinical laboratory studies, assay performance studies, clinical studies, and clinical utility studies were conducted.

A. Preclinical studies

Preclinical laboratory studies were conducted to determine the identity and specificity of the reagents.

1. Characterization of the antigen

Purity and identity of the PSA used to immunize goats and in the affinity purification of the goat polyclonal antibody were characterized by SDS polyacrylamide gel electrophoresis and amino acid analysis. The results from these studies showed agreement with values previously reported in the literature for purified PSA.[1 - 4]

2. Characterization of Antibodies

The DPC PSA IRMA anti-PSA monoclonal(mouse) antibody was characterized with respect to subclass type and affinity constant. Specificity of the anti-PSA monoclonal antibody was demonstrated by the presence of a single band in a Western blot. Specificity of DPC PSA IRMA polyclonal (goat) antibody was also demonstrated. These studies confirmed the specificity of the antibody pair used in the DPC PSA IRMA. Interferences from substances commonly found in patient sera, from chemotherapeutic drugs and from other drugs potentially used in the prostatic cancer patients were evaluated. No cross reactivity was observed at any concentration spanning the anticipated levels of alpha fetoprotein, carcinoembryonic antigen, ferritin, prolactin, triglycerides, or total human serum protein. No crossreactivity was observed at any concentration spanning the anticipated serum levels of cyclophosphamide, diethylstilbestrol, doxorubicin, methotrexate, megesterol, flutamide, lupon, estramustine, hydroxyflutamide, or at high concentrations of 24 other non-chemotherapeutic drugs.

B. Assay Performance

Assay performance studies were conducted to determine the performance characteristics of the assay.

1. Reproducibility

Within run (intra-assay), between run (inter-assay), between laboratory, and between lot reproducibility was evaluated in a series of assay

runs of the DPC PSA IRMA at Diagnostic Products Corporation and three outside sites using the same three lots of reagents. Samples prepared by enriching serum with various amounts of PSA were analyzed by the DPC PSA IRMA. Each specimen was analyzed in replicates of six per assay. Assays at each of the four sites were repeated five times with each of three lots for a total of 60 assays. The coefficient of variation (CV) for intra-assay, inter-assay, inter-laboratory site, and inter-lot sources of variation is given at four different clinically important PSA levels:

Mean intra-assay CV's

5% at approximately 2 ng/mL (range 4 to 6%);
3% at approximately 5 ng/mL (range 2 to 4%);
3% at approximately 10 ng/mL (range 2 to 4%);
3% at approximately 25 ng/mL (range 2 to 4%)

Mean inter-assay CV's

7% at approximately 2 ng/mL (range 4 to 12%);
5% at approximately 5 ng/mL (range 1 to 8%);
4% at approximately 10 ng/mL (range 3 to 7%);
5% at approximately 25 ng/mL (range 2 to 9%)

Mean inter-laboratory site CV's

5% at approximately 2 ng/mL (range 3 to 6%);
4% at approximately 5 ng/mL (range 4 to 5%);
6% at approximately 10 ng/mL (range 5 to 8%);
5% at approximately 25 ng/mL (range 4 to 5%)

Mean inter-lot CV's

2.5% at approximately 2 ng/mL (range 1 to 5%);
3% at approximately 5 ng/mL (range 1 to 4%);
4% at approximately 10 ng/mL (range 2 to 5%);
3% at approximately 25 ng/mL (range 2 to 3%)

In addition, 81 DPC PSA IRMA assays were conducted on combinations of three lots of antibody coated tubes, labeled antibody, calibrators, and assay buffer. CV's were calculated for the PSA values obtained for controls assayed in all 81 assays. These CV's represented all sources of variability combined, including within-assay, between assay, and between-lot. Coeffients of variation were less than 10% for analyte levels of 2-80 ng/mL. These CVs are acceptable for an assay of this type.

2. Analytical Sensitivity

The sensitivity of the DPC PSA IRMA is calculated to be approximately 0.1 ng/mL. This concentration is defined as the concentration at two standard deviations above the DPC PSA IRMA "A" or "Zero" Calibrator and represents the lowest measurable concentration of PSA that can be distinguished from zero, also noted as the detection limit or minimal detectable dose.

3. Parallelism

Multiple dilution of each of 21 specimens from prostate cancer patients containing elevated PSA concentrations were assayed by the DPC PSA IRMA undiluted and diluted with the zero calibrator. Linear regression analysis of PSA concentration as a function of dilution yielded correlation coefficients of 0.9986 or better for all specimen. The mean observed/expected value for the dilutions was 106 percent. The coefficient of variation for the PSA concentrations calculated from the dilutions yielded a mean of 4.1 percent, and ranged from 2 to 7 percent.

4. Recovery

Varying concentrations of PSA were added to eight prostate cancer serum samples. The endogenous and spiked concentrations of PSA in each sample were assayed using the DPC PSA IRMA. The percent recoveries were calculated and found to range from 88-100 percent with a mean recovery of 96 percent.

5. Potential interference

Spiking recovery interference studies revealed that neither icterus (20 mg/dL bilirubin) nor hemolysis (30 uL hemolyzed packed red cells) had any clinically significant effect on the DPC PSA IRMA assay.

6. Method Comparison Study

Correlation and linear regression analyses were applied to serum PSA measurements obtained by the DPC PSA IRMA assay and the comparison immunoassay for which an approved premarket application for the measurement of PSA exists. Test results of 2700 serum specimens, with PSA levels ranging from 0 to approximately 6000 ng/mL, were analyzed using

linear regression. The resulting correlation coefficient was 0.987, the slope was 1.035, and the intercept was - 1.627 ng/mL.

7. Stability

PSA Calibrators, PSA Assay Buffer, PSA Ab-Coated Tubes, Buffered Wash Solution, and Iodine-125 labeled anti-PSA murine monoclonal antibody were subjected to stability studies. These included elevated temperatures for varying numbers of days, conditions recommended for use in the package insert for varying numbers of days, and under conditions used in-house for long term storage for varying numbers of days. Following the indicated conditions, the components were tested in an assembled kit format using the DPC PSA IRMA assay.

No deterioration was observed in the reagents under the conditions of the stability studies. The data support one year shelf-life for calibrators, assay buffers, Ab-coated tubes, buffered wash solution; 60 days of shelf-life for I 125 labeled anti-PSA monoclonal antibody and 60 days for the DPC PSA IRMA assay stored at 2-8° C.

Serum samples should be stored at 2-8° C if they are to be assayed within 24 hours. If samples are to be assayed after extended storage, samples should be stored at -20° C.

C. Clinical Studies

Clinical studies were performed at three medical institutions to determine PSA values using DPC PSA IRMA assay and to demonstrate comparability of the method of quantitation to another device for which there is an approved PMA.

The three investigators who conducted these studies were: Lynn Witherspoon, M.D., Ochsner Clinic, New Orleans, LA; Robert Vessella, Ph.D., University of Washington, Department of Urology, Seattle, WA; and Herbert A. Fritsche, Ph.D., M.D., Anderson Cancer Center, Division of Laboratory Medicine, University of Texas, Houston, TX.

Serum specimens (2710) were obtained from a total of 1578 subjects and patients consisting of 470 healthy male subjects with negative digital rectal exams, 204 female subjects, 363 male patients with nonmalignant diseases, 131 patients with non-prostatic malignancies,

and 410 patients with prostatic malignancies. Serial serum specimens were obtained from 166 patients with malignancies (161 prostatic cancer; 5 colon cancer). The distribution of the PSA values in these 1578 individuals is shown in TABLE 1. The nonmalignant conditions included BPH, prostatitis, and benign diseases of the colon, bladder, liver, pancreas, testes, lung, kidney, and central nervous system. The malignant conditions included testicular, pancreatic, bladder, colon, kidney, liver, pulmonary, renal, pancreatic, rectal, and stomach cancers.

The distribution of serum PSA levels from healthy individuals and patients with nonmalignant and malignant disease are presented in TABLE 1. The distribution of serum PSA values using the DPC PSA IRMA in healthy subjects and patients with nonmalignant and malignant disease matched closely the distribution of PSA values using the comparison method (98.6 percent).

A summary of the correlation between the DPC PSA IRMA and the comparison method is presented in TABLE 2. The number of specimens listed represents the number of specimens available for testing by both the DPC PSA IRMA and comparison method which were included in the analysis.

TABLE 1

Distribution of PSA by DPC PSA IRMA
All Investigational Sites

		PSA(ng/mL)				
Patient Category		0.00-4.00	4.01-10.00	10.01-20.00	20.01-40.00	> 40.00
Healthy Male Subjects	470	468	2	0	0	0
Female Subjects	204	204	0	0	0	0
Non-malignant Diseases	363	305	44	10	2	2
Non-Prostatic Malignancies	131	115	12	1	1	2
Prostate Cancer	410	247	63	29	23	48
Total	1578	1339	121	40	26	52

For serially monitored patients, this table includes only the 1st available specimen.

Table 2
Summary of Correlation studies

Specimen Type	N	Corr. Coeff.	Slope	Y-Intercept
Healthy Male Subjects	470	0.93	0.942	0.018
BPH Patients	308	0.99	0.996	-0.032
Nonprostate Cancer Patients	124	0.99	1.012	-0.017
Prostate Cancer Patients	1518	0.99	1.036	-2.843

D. Clinical Utility as Demonstrted by Serial Samples

Clinical studies were performed to evaluate DPC PSA IRMA to aid in the management of patients diagnosed with prostate cancer.

Serial samples from 161 patients clinically diagnosed with prostate cancer were assayed retrospectively by both the DPC PSA IRMA and a comparison method for which there is an approved PMA. Monitoring studies included 106 patients from New Orleans, 25 patients from University of Washington, and 30 patients from M.D.Anderson Cancer Center.
Of the 161 patients with prostate cancer, 36 patients initially presented at diagnosis with stage A disease, 29 with stage B disease, 22 patients with stage C disease, and 65 patients with stage D disease. One patient was diagnosed with oat cell carcinoma and there was no stage information for eight patients.

Serial measurement of PSA concentrations using both the DPC PSA IRMA and the comparison method reflected the progression or remission of the disease in 145 of the 152 cases (95.4 percent) which could be classified into one of 6 clinical groups. The nine cases which could not be classified into one of the six clinical groups nevertheless showed the same trends over time with both methods.

The results of the studies are summarized as follows:

1. 19 patients' serum PSA concentrations decreased following effective therapy,

2. 49 patients' serum PSA concentrations remained in the normal reference range in the absence of active or progressive disease,

3. 29 patients' serum PSA concentrations were or became elevated above the normal reference range in the presence of active or progressive disease,

4. 48 patients' serum PSA concentrations paralleled the clinical course of the disease with periods of disease progression and periods of response to therapy,

5. 5 patients' serum PSA concentrations were elevated above the normal reference range in the absence of clinically detectable disease or while the patient was in remission, and

6. 2 patients' serum PSA concentrations were in the normal reference range in the presence of clinically progressive disease.

VIII. Conclusions drawn from the studies

The foregoing studies have demonstrated the safety and effectiveness of DPC PSA IRMA to determine the concentration of PSA in human serum to aid in the management of prostate cancer patients. Based upon the results of preclinical studies, assay performance (reproducibility, analytical sensitivity, parallelism, recovery, potential interference, method comparison, and stability), clinical correlation, and clinical utility studies cited above, the DPC PSA IRMA performance specifications are within acceptable limits for a device of this type.

The distribution of PSA concentrations as determined by the DPC PSA IRMA demonstrates agreement with the values obtained with a device for which there is an approved PMA.

The data from the serially monitored prostate cancer patients support the clinical utility of the DPC PSA IRMA as a test to aid in the management of prostate cancer.

Based on the data provided in the PMA, CDRH has concluded that the device is reasonably safe and effective for the stated indications.

IX. Panel Recommendation

Pursuant to section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Immunology Devices Panel for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

X. CDRH Action on the application

CDRH issued an approval order for applicant's PMA for Coat-A Count® PSA IRMA to Diagnostic Products Corporation on SEP 15 1995.

The applicant's manufacturing facilities were inspected on May 5, 1995 and the facilities were found to be in compliance with the Good Manufacturing Practice (GMP) Regulations.

The shelf-life of the DPC PSA IRMA and I 125 labeled anti-PSA monoclonal antibody has been established at 60 days and one year for calibrators, assay buffers, Ab-coated tubes and buffered wash solution when stored at 2°- 8°C.

XI. Approval Specifications

Direction for Use: See attached labeling (Attachment A).

Conditions of approval: CDRH approval of this PMA is subject to full compliance with the conditions described in the approval order (Attachment B).

XII. References

1. Wang, M.C., et al., Purification of a human prostate specific antigen. Investigative Urology 17:159 (1979).

2. Kuriyama, M. et al., Prostatic acid phosphatase and prostate-specific antigen in prostate cancer in Prostate Cancer in International Advances in Surgical Oncology 5:29 (1982), Alan R. Liss, Inc. New York.

3. Watt, WK, Lee P-J, et al., Human prostate-specific antigen: structural and functional similarity with serine proteases. Proc Natl Acad Sci USA; 83:3166 (1986).

4. Lundwall A., Characterization of the gene for prostate specific antigen, a human glandular kallikrein Biochem Biophys Res Commun; 161:1151 (1989).

5. Papsidero, L.D., et al., A prostate antigen in sera of prostatic cancer patients. Cancer Research 40:2428 (1980).

6. Nadji, M., et al., Prostatic-specific antigen: an immunohistologic marker for prostatic neoplasms. Cancer 48:1229 (1981).

7. Wang, M.C., et al., Prostate antigen of human cancer patients. In Methods in Cancer Research 19:179 (1982), Academic Press, Inc.

8. Kuriyama, M., et al., Quantitation of prostate-specific antigen in serum by a sensitive enzyme immunoassay. Cancer Research 40:4658 (1980).

9. Brawer, M.K. and Lange, P. H., Prostate-specific antigen: its role in early detection, staging, and monitoring prostatic carcinoma. J Endocrinology 3:227 (1989).

10. Killian, et al., Prognostic importance of prostate-specific antigen for monitoring patients with stages B2 to D1 prostate cancer. Cancer Research 45:886(1985).

11. Stamey, T.A., Prostate specific antigen in the diagnosis and treatment of adenocarcinoma of the prostate. Urology 10:50 (1989).

12. Ercole, C.J. et al., Prostatic specific antigen and prostatic acid phosphatase in the monitoring and staging of patients with prostatic cancer. J Urology 138:1181 (1987).

13. Chan, D.W., et al., Prostate-specific antigen as a marker for prostatic cancer: a monoclonal and a polyclonal immunoassay compared. Clin. Chem 33:1916 (1987)

14. Lange, P.H. et al., The value of serum prostate specific antigen determinations before and after radical prostatectomy. J Urology 141:873 (1989).

15. Oesterling, J.E., Prostate specific antigen: a critical assessment of the most useful tumor marker for adenocarcinoma of the prostate. J. Urology 145:907 (1991).

16. Kuriyama, M. et al., Multiple marker evaluation in human prostate cancer with the use of tissue-specific antigens. J Nat Cancer Institute 68:99 (1982).

17. Morgan, W.R. et al., Prostate specific antigen values after radical retropubic prostatectomy for adenocarcinoma of the prostate: impact of adjuvant treatment (hormonal and radiation). J Urol 145:319 (1991).

18. Stamey, T.A., Yang, N., et al., Prostate specific antigen as a serum marker for adenocarcinoma of the prostate. N Engl J Med 317:909 (1987).

19. Brawer, M.K., et al., The effect of digital rectal examination on serum levels of prostatic specific antigen. Arch Pathol Lab Med 112:1110 (1988).

20. Hughes, H.R. et al., Serum prostatic specific antigen: In vitro stability and the effect of ultrasound rectal examination in vivo. Ann Clin Biochem 24:(Suppl)206 (1987).

COAT-A-COUNT®

PSA IRMA

Caution: Federal law restricts this device to sale by or on the order of a physician.

DPC

Coat-A-Count® PSA IRMA

Intended Use

Coat-A-Count PSA IRMA is an immunoradiometric assay intended for the quantitative measurement of prostate-specific antigen (PSA) in serum to aid in the management of prostate cancer patients.

Catalog numbers: **IKPS1** (100 tubes), **IKPS2** (200 tubes)

The 100-tube kit contains not more than 20 microcuries (740 kilobecquerels) of radioactive ^{125}I monoclonal anti-PSA; the 200-tube kit contains not more than 40 microcuries (1480 kilobecquerels).

The concentration of PSA in a given specimen determined with assays from different manufacturers can vary due to differences in assay methods and reagent specificity. The results reported by the laboratory to the physician must include the identity of the assay used. Values obtained with different PSA assays cannot be used interchangeably. Before changing assays, the laboratory must confirm the baseline values for patients being serially monitored.

Summary and Explanation of the Test

Prostate specific antigen (PSA), first identified and characterized by Wang et al in 1979, is a glycoprotein monomer with protease activity.[1,2] PSA has an isoelectric point of approximately 6.9 and a molecular weight of approximately 33-34 kilodaltons, containing approximately 10% carbohydrate by weight.[1,2] Subsequently, the amino acid sequence of PSA was reported,[3] and the gene has been cloned.[4] PSA is biochemically and immunologically distinct from PAP and does not exhibit enzymatic phosphatase activity.[5]

PSA is localized in the cytoplasm of prostatic ductal epithelium and in secretions of the ductal lumina.[6] Because PSA is a secretory protein of the prostate, it can be recovered and purified both from prostatic tissue and from seminal plasma.[7] PSA has been found to be exclusively associated with prostate tissue, and elevated serum PSA has been found in patients with prostate cancer, benign prostatic hypertrophy, and inflammatory conditions of other adjacent genitourinary tissues, but not in healthy men, men with nonprostatic carcinoma, healthy women or women with cancer.[5,8]

Serum PSA is not suitable as a screen for prostate cancer because elevated PSA concentrations are also observed in patients with benign prostatic hypertrophy.[8]

PSA determinations can be useful in detecting metastatic or persistent disease in patients following surgical or medical treatment of prostate cancer.[9,10] Persistent elevation of PSA following treatment or an increase in the pretreatment PSA concentration is indicative of recurrent or residual disease.[11-15] Hence, PSA is widely accepted as an aid in the management of prostate cancer patients.[11-15] Concurrent measurement of PAP may contribute additional information.[16]

Principle of the Procedure

Coat-A-Count PSA IRMA is a solid-phase immunoradiometric assay based on monoclonal and polyclonal anti-PSA antibodies: one ^{125}I-labeled anti-PSA monoclonal antibody in liquid phase, and one polyclonal anti-PSA antibody immobilized to the wall of a polystyrene tube.

- PSA is captured between polyclonal anti-PSA antibodies immobilized on the inside surface of the polystyrene tube and the radio-labeled monoclonal anti-PSA tracer.
- Unbound ^{125}I-labeled anti-PSA antibody is removed by decanting the reaction mixture and washing the tube; this reduces nonspecific binding to a very low level, and ensures low-end precision.
- The PSA concentration is directly proportional to the radioactivity present in the tube after the wash step. The radioactivity is counted using a gamma counter, after which the concentration of PSA in the patient sample is obtained by comparing the patient counts-per-minute with those obtained for the set of calibrators provided.

Procedure

There are only two reagents to dispense, and total incubation time is 1 hour. The tracer has a high specific activity, with total counts of approximately 300,000 cpm at iodination. No centrifuge is required. The Coat-A-Count procedure is suitable for high-volume testing.

Separation

The coated-tube methodology offers significant advantages in reliability, as well as speed and convenience, since the tubes can be vigorously decanted without loss of antibody-bound material. This results in a clean separation of bound from free, with negligible nonspecific binding.

Calibration

The assay has a calibration range of 1.5 to 150 ng/mL.

Precision

CVs are low and uniform. The assay can detect as little as 0.1 ng/mL, and no "end-of-run" effect has been observed in assays involving up to 200 tubes.

Accuracy

Extensive experiments have shown that the assay is accurate over a broad range of PSA values. Its accuracy has been further verified in a patient comparison study against a commercially available immunoradiometric assay for PSA.

Specificity

The kit is specific for PSA, with low crossreactivity to other proteins and polypeptides present in patient samples.

Warnings

- For *in vitro* diagnostic use.
- Some individuals have antibodies to mouse protein which can cause interference in immunoassays that employ antibodies derived from mice. Specimens from patients who have received preparations of mouse monoclonal antibodies for diagnosis or therapy, in particular, may contain human anti-mouse antibodies (HAMA). These specimens may show erroneous results in such assays.[20-22] Therefore, Coat-A-Count PSA IRMA results should be used only in conjunction with results from some other diagnostic procedure and information available from the clinical evaluation of the patient.

Precaution

- Before opening the kit, review the paragraphs on safety printed on the inside front cover, as they relate to the safe handling and disposal of reagents containing radioactivity, human serum and sodium azide.

Materials Supplied: Initial Preparation

PSA Ab-Coated Tubes (IPS1)

100 (200*) polystyrene tubes coated with goat polyclonal antibodies to PSA and packaged in zip-lock bags. Store refrigerated and protected from moisture, carefully resealing the bags after opening: stable at 2–8°C until the expiration date marked on the bag.

^{125}I PSA Ab (IPS2)

Two vials (four vials*) of lyophilized reagent, consisting of an iodinated anti-PSA murine monoclonal antibody, with preservative. Reconstitute each vial by adding a measured **5.5 mL** distilled water. Let stand for 10 minutes, then mix by gentle inversion. Store refrigerated: stable at 2–8°C for at least 30 days after reconstitution, or until the expiration date marked on the label.

PSA Calibrators (PSI3–9)

One set of seven vials, labeled A through G, of PSA calibrators in a non-human serum/buffer matrix, with preservative. The calibrators are supplied in liquid form, ready to use. The zero calibrator A contains 3 mL, while the remaining calibrators B through G each contain 1 mL. Store refrigerated: stable at 2–8°C for at least 30 days after opening. The life of the calibrators may be extended by freezing. Aliquot if necessary to avoid repeated freezing and thawing.

The calibrators contain, respectively, 0, 1.5, 3, 10, 50, 100 and 150 nanograms of PSA per milliliter (ng/mL). Intermediate calibration points may be obtained by mixing calibrators in suitable proportions.

PSA Assay Buffer (PSAB)

One vial (two vials*) containing 11 mL of buffered diluent with preservative. Store refrigerated: stable at 2–8°C for at least 30 days after opening, or until the expiration date marked on the vial.

Buffered Wash Solution Concentrate (2PSBW)

One vial (two vials*) each containing 60 mL of a concentrated buffered saline solution, with surfactants and sodium azide as a preservative. Using a transfer container, dilute each vial of concentrate with **600 mL** distilled water, for a total volume of 660 mL. Store refrigerated: stable at 2–8°C for at least 6 months after preparation.

* 200-tube kit.

Materials Required But Not Provided

- Gamma counter – compatible with standard 12×75 mm tubes
- Rack shaker – set at approximately 200 strokes per minute. Available from DPC as catalog numbers DPSR1 (110 VAC) and DPSR2 (220 VAC).

Reagent Preparation

- Distilled or deionized water
- Pipet – to deliver 5.5 mL
- Graduated cylinder – for dispensing 600 mL
- Plastic storage container with lid – for preparation and storage of Buffered Wash Solution

Immunoassay

- Micropipets: 50 µL and 100 µL. For the 100 µL reagent additions, a reliable repeating dispenser (Nichiryo Model 8100 or equivalent) is recommended – available from DPC.
- Dispenser – for delivering 2.0 mL of Buffered Wash Solution. A 2.0 mL dispenser is available from DPC as catalog number DB2ML.
- Foam decanting rack – available from DPC.

Specimen Collection

The patient need not be fasting, and no special preparations are necessary. Collect blood by venipuncture into plain tubes, taking care to avoid hemolysis, and separate the serum from the cells. Note the time of collection. The procedure calls for 50 µL per tube.

Neither bilirubin nor hemolysis interferes with the assay.

Samples should be obtained before biopsy, prostatectomy or prostatic massage, since manipulation of the prostate gland may lead to elevated PSA levels persisting for up to 3 weeks.[17] Studies have shown conflicting results on the existence of an effect of digital rectal examination on PSA level.[18,19] Therefore, when possible, obtain PSA samples prior to digital rectal examination.

Store serum samples at 2–8°C if they are to be assayed within 24 hours. Store at –20°C or colder if samples are to be assayed after extended storage. Before assay, allow the samples to come to room temperature and mix by *gentle* swirling or inversion. Aliquot, if necessary, to avoid repeated thawing and freezing. Do *not* attempt to thaw frozen specimens by heating them in a waterbath. Dilute patient samples with high concentrations in the zero calibrator before assay, so that the response falls within the calibration range of the assay.

Immunometric Assay Procedure

All components must be at room temperature (18°C – 27°C) before use.

1 Label fourteen PSA Ab-Coated Tubes A (nonspecific binding) and B through G ("maximum binding") in duplicate. Label additional antibody-coated tubes, also in duplicate, for controls and patient samples.

Calibrators	ng/mL
T*	—
A (NSB)	0
B	1.5
C	3
D	10
E	50
F	100
G(MB)	150

* Optional

2 Pipet **50** µL of each calibrator, control and patient serum sample into the tubes prepared.

Pipet directly to the bottom. *Patient samples expected to contain high concentrations should be diluted in the zero calibrator before assay. The use of disposable-tip micropipets is recommended, to avoid carryover from sample to sample. Positive-displacement pipets and automatic pipettor-diluters should be used only if the possibility of carryover has been evaluated and found to be insignificant.*

3 Add **100** µL of PSA Assay Buffer to all tubes (except T).

Pipet directly to the bottom. *Make sure that sample and buffer are in solution and thoroughly mixed, without foaming. A repeating dispenser (Nichiryo or equivalent) is recommended.*

4 Shake for **30 minutes** on a rack shaker.

5 Decant thoroughly. Add **2 mL** Buffered Wash Solution to each tube. Wait 1 to 2 minutes, then decant thoroughly.

Removing all visible moisture will greatly enhance precision. Using a foam decanting rack, decant the contents of all tubes (except the T tubes) and allow them to drain for 2 or 3 minutes. Then strike the tubes sharply on absorbant paper to shake off all residual droplets.

6 Add **100** µL of ^{125}I PSA Ab to every tube.

Set the (optional) T tubes aside for counting (at step 9); they require no futher processing.

7 Shake for **30 minutes** on a rack shaker.

8 Decant thoroughly. Add **2 mL** Buffered Wash Solution to each tube. Wait 1 to 2 minutes, then decant thoroughly. Again add **2 mL** Buffered Wash Solution, wait 1 to 2 minutes, and decant thoroughly.

Removing all visible moisture will greatly enhance precision. Using a foam decanting rack, decant the contents of all tubes and allow them to drain for 2 or 3 minutes. Then strike the tubes sharply on absorbant paper to shake off all residual droplets.

9 Count for **1 minute** in a gamma counter.

In multi-head gamma counters, the (optional) Total Counts tubes should be separated from the remaining assay tubes by at least one space, to minimize the possibility of spillover.

Calculation and Quality Control

To calculate PSA concentrations from a log-log representation of the calibration curve, first correct the counts per minute (CPM) of each pair of tubes by subtracting the average CPM of the nonspecific binding tubes (calibrator A):

Net Counts = Average Counts *minus* Average **NSB** Counts

Then determine the binding (%B/B_{150}, here called "%B/MB") of each pair of tubes as a percent of maximum binding, with the NSB-corrected counts of the highest calibrator (calibrator G) taken as 100%:

Percent Bound = (Net Counts / Net **MB** Counts) × 100

Using the 3-cycle log-log graph paper supplied with the kit, plot Percent Bound versus Concentration for each of the nonzero calibrators, and draw a curve approximating the path of these points. (Connect the calibration points with arcs or straight line segments. Do not attempt to fit a single straight line to the data.) PSA concentrations for controls and unknowns within range of the nonzero calibrators may then be estimated from the calibration curve by interpolation. An additional plot of Percent Bound versus Concentration for the three lowest calibrators on linear-linear graph paper may be used for interpolation near zero dose.

Comments: Although other approaches are acceptable, data reduction by the method just described has certain advantages from the standpoint of quality control. In particular, it yields a calibration curve that is *relatively* linear in both log-log and linear-linear representations, and relatively stable from assay to assay. It also yields valuable QC parameters, namely, Percent Bound (%B/B_{150} or "%B/MB") values for the nonzero calibrators.

A still more informative graph, conveying a sense of within-assay reproducibility as a function of concentration, can be obtained by plotting the Percent Bound values of individual calibrator tubes directly, i.e. without first averaging the CPM of replicates.

Alternatives: Although Percent Bound can be calculated directly from Average CPM, correction for nonspecific binding usually produces a calibration curve that is more nearly linear throughout its range. A calibration curve can also be constructed by plotting CPM or Average CPM directly against Concentration on either log-log or linear-linear graph paper. (Semi-log graph paper should *not* be used.) This approach has the virtue of simplicity, but is less desirable from the standpoint of quality control.

Computerized Data Reduction: "Point-to-point" methods, including linear and cubic spline fits, are suitable for use with the Coat-A-Count PSA IRMA system. However, since they provide little assistance in monitoring the integrity of an assay, it is important to prepare the recommended log-log plot of the calibration curve, either manually or by computer, as a quality control step.

Data reduction techniques based on the logistic model may also be applicable. Within this family, curve-fitting routines based on the 4- or 5-parameter logistic are the most suitable candidates. Bear in mind, however, that some algorithms currently in use may not converge successfully, even when the logistic model is true to the data. If a logistic method is adopted, it is essential to verify its appropriateness for each day's assay by monitoring the backcalculation of the calibrators, and other parameters. In addition, a plot of the calibration curve in a log-log representation is highly recommended, as this is more informative than the conventional semi-log plot.

Sample Handling: The instructions for handling and storing patient samples and components should be carefully observed. Dilute patient samples with high concentrations in the zero calibrator before assay. All samples, including the calibrators and controls, should be assayed in duplicate. It is important to use a *disposable-tip* micropipet, changing the tip between samples, to avoid carryover contamination. Positive-displacement pipets and automatic pipettor-diluters should be used only if the possibility of carryover has been evaluated and found to be insignificant. Pairs of control tubes may be spaced throughout the assay to help verify the absence of significant drift. Inspect the results for agreement within tube pairs, and take care to avoid carryover from sample to sample.

Gamma Counter: To minimize the possibility of spillover in multi-well gamma counters, the (optional) total counts tubes (T) should be separated by one or more spaces from the other assay tubes. Alternatively, add only 25 µL of the ^{125}I PSA Ab to each of the T (total counts) tubes at step 6, and multiply the observed counts per minute in these tubes by 4.

Controls: Controls or serum pools with at least two PSA concentration levels (low and high) should routinely be assayed as unknowns, and the results charted from day to day as described in Westgard JO, et al. A multi-rule chart for quality control. Clin Chem 1981;27:493-501. Repeat samples are a valuable additional tool for monitoring interassay precision.

QC Parameters: We recommend keeping track of these performance measures:

T = Total Counts (as counts per minute)

%NSB = 100 × (Average NSB Counts / Total Counts)

%MB = 100 × (Net MB Counts / Total Counts)

And the Percent Bound (%B/B_{150} or "%B/MB") values of all but the highest of the nonzero calibrators, for example:

%C/MB = 100 × (Net Calibrator "C" Counts) / (Net MB Counts).

Record Keeping: It is good laboratory practice to record for each assay the lot numbers and reconstitution dates of the components used, as well as control results and QC parameters.

Further Reading: A technical bulletin titled "Coat-A-Count TSH IRMA: Notes on Data Reduction, QC and Optimization" (catalog number: ZJ019) is available on request. See Dudley RA, et al. Guidelines for immunoassay data reduction. Clin Chem 1985;31:1264-71.

Example

The values below are intended for illustration only and should not be used to calculate results from another assay.

Tube	Duplicate CPM	Average CPM	Net CPM	Percent Bound	PSA ng/mL
T	261,413 259,305	260,359			
A (NSB)	287 208	256	0		0
B	1,677 1,588	1,633	1,377	1.5%	1.5
C	2,865 2,814	2,840	2,584	2.9%	3
D	9,128 8,848	8,988	8,732	9.7%	10
E	40,028 39,017	39,523	39,267	44%	50
F	67,069 66,631	66,850	66,594	74%	100
G ("MB")	90,231 88,810	89,521	89,265	100%	150
Unknowns					
X1	2,103 2,086	2,095	1,839	2.0%	2.1
X2	4,203 4,151	4,177	3,921	4.4%	4.5
X3	18,678 18,075	18,377	18,121	20%	22

Quality Control Parameters:
T = 260,359 cpm
%NSB = 0.10%
%MB = 35%

Performance Data

In the sections below, PSA results are expressed as nanograms of PSA per milliliter (ng/mL).

Precision

The reliability of DPC's Coat-A-Count PSA IRMA procedure was assessed by examining its reproducibility on samples selected to represent a range of PSA levels.

Intraassay (Within-Run): Statistics were calculated for each of three samples from the results of 20 pairs of tubes in a single assay. Results are expressed in ng/mL.

Sample	Mean	SD	CV
1	2.3	0.10	4.3%
2	4.5	0.24	5.3%
3	24	0.83	3.5%

Interassay (Run-to-Run): Statistics were calculated for each of three samples from the results of pairs of tubes in 20 different assays. Results are expressed in ng/mL.

Sample	Mean	SD	CV
1	2.3	0.09	3.9%
2	4.6	0.20	4.3%
3	24	0.92	3.8%

Sensitivity

The assay's detection limit, defined as the concentration two standard deviations above the response at zero dose, is approximately 0.1 ng/mL.

Drift

To determine whether there is any position (or "end-of-run") effect due to delays in the addition of reagents, pairs of tubes were spaced throughout a long assay for each of six samples. The results show no significant position effect even in assays of up to 200 tubes.

Sample	Tubes 17–28	Tubes 69–80	Tubes 121–132	Tubes 187–198
1	2.1	2.2	2.3	2.2
2	2.8	2.9	3.0	2.8
3	4.3	4.6	4.5	4.5
4	20	20	21	21
5	23	23	23	24
6	41	41	42	42

Specificity

The specificity of the CAC PSA IRMA was analyzed by testing sera containing the compounds tabulated below. These compounds did not show interference, either positive or negative, at the levels indicated.

Compound	Amount Added
Interfering substances:	
Albumin	9 g/dL
Alpha-fetoprotein (AFP)	10,000 ng/mL
Carcinoembryonic antigen (CEA)	10,000 ng/mL
Ferritin	10,000 ng/mL
Human chorionic gonadotropin (HCG)	10,000 mIU/mL
Human IgG	1,600 mg/dL
Prostatic acid phosphatase (PAP)	1,000 ng/mL
Prolactin	2,000 ng/mL
Triglycerides	2,000 mg/dL
Protein	16.5 g/dL
Chemotherapeutic agents:	
Cyclophosphamide	1,000 µg/mL
Diethylstibesterol	10,000 ng/mL
Doxorubicin HCL	100 µg/mL
Methotrexate	100 µg/mL
Megesterol acetate	1,000 µg/mL
Flutamide	100 µg/mL
Lupron	100 µg/mL
Estramustine	1,000 µg/mL
Hydroxyflutamide	100 µg/mL

In addition, the specificity of the Coat-A-Count PSA IRMA was also analyzed by testing sera containing the compounds listed below. These compounds did not show interference, either positive or negative, at the level of 100,000 ng/mL.

Acetaminophen	Furosemide
Acetylsalicyclic acid	Gentamicin
Albuterol	Hydrochlorothiazide
Alprazolam	Hydromorphone
Aminophylline	Ibuprofen
Amitryptylline	Indomethacin
Ascorbic acid	Metaproterenol
Atropine	Morphine
Caffeine	Phenobarbital
Clorpropamide	Phenylpropanolamine
Codeine	Secobarbital
Diazepam	Theophylline

Parallelism

Four patient serum samples were assayed both undiluted and diluted with the zero calibrator. The observed and expected values are presented below in ng/mL.

Sample	Dilution	O Observed	E Expected	%O/E
1	20 in 20	50	—	—
	10 in 20	26	25	104%
	4 in 20	10	10	100%
	2 in 20	5.3	5.0	106%
	1 in 20	2.7	2.5	108%
2	20 in 20	66	—	—
	10 in 20	33	33	100%
	4 in 20	14	13	108%
	2 in 20	7.1	6.6	108%
	1 in 20	3.6	3.3	109%
3	20 in 20	80	—	—
	10 in 20	40	40	100%
	4 in 20	16	16	100%
	2 in 20	8.3	8.0	104%
	1 in 20	4.2	4.0	105%
4	20 in 20	126	—	—
	10 in 20	65	63	103%
	4 in 20	27	25	108%
	2 in 20	14	13	108%
	1 in 20	7.0	6.3	111%

Spiking Recovery

Three spiking solutions were prepared using the zero calibrator as diluent. The solutions (A, B and C) were made to represent 60, 261 and 575 ng/mL, respectively. A 50 µL aliquot of each solution was spiked into 950 µL aliquots of four different patient serum samples, for a spiking ratio of 1 to 19, leaving the serum matrix of the spiked samples relatively intact. All samples were then assayed by the Coat-A-Count PSA IRMA procedure. To calculate expected values, 95% of the unspiked value was added to 5% of the spiking solution concentration (3.0, 13 and 29 ng/mL, respectively).

Sample	Spiking Solution	O Observed	E Expected	% O/E
1	—	1.5	—	—
	A	4.3	4.4	98%
	B	14	14	100%
	C	29	30	97%
2	—	42	—	—
	A	42	43	98%
	B	51	53	96%
	C	63	69	91%
3	—	86	—	—
	A	81	85	95%
	B	90	95	95%
	C	109	110	99%
4	—	106	—	—
	A	100	104	96%
	B	109	114	96%
	C	123	129	95%

Method Comparison

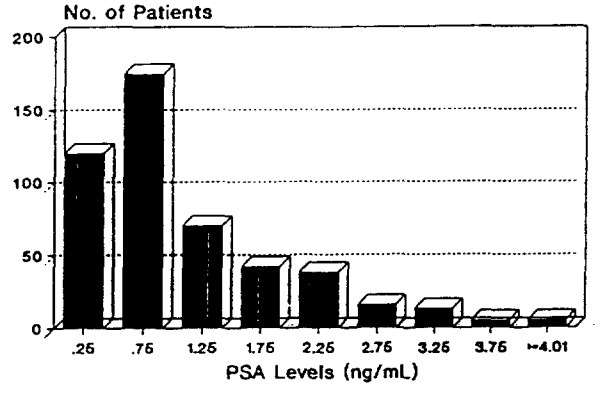
A method comparison study was conducted at three clinical sites involving 2,604 specimens with PSA concentrations within the calibration range of the Coat-A-Count PSA IRMA and the reference assay. Subjects included prostatic cancer patients (single specimens and serial specimens); patients with benign prostatic disease, other nonmalignant diseases, nonprostatic cancers; and individuals with normal digital rectal exams. 204 female subjects were also included. Linear regression analysis yielded the following statistics.

(CAC IRMA) = 0.99 (Reference Assay) + 0.171 ng/mL $r = 0.987$

Mean: 5.4 ng/mL (CAC IRMA)
5.3 ng/mL (Reference Assay)

Expected Values

PSA values were studied in 470 healthy male subjects with normal digital rectal exams studied at three clinical sites. Approximately 97% of the subjects were over 40 years of age. The distribution of PSA values measured by DPC's Coat-A-Count PSA IRMA is shown below. 468 out of 470 subjects (99.5%) had PSA values of less than 4 ng/mL. Based upon this distribution, an upper limit of normal of 4 ng/mL was established.



Laboratories should consider the reference range limit suggested by this study *as a guideline only*. Because of differences which may exist between laboratories and locales with respect to population, laboratory technique and selection of reference groups, it is important for each laboratory to establish by similar means the appropriateness of adopting the reference range suggested here.

Limitations

1 Serum PSA concentrations should not be interpreted as absolute evidence for the presence or absence of malignant disease, nor should serum PSA be used as a screening test for malignant disease.[8]

2 Prediction of malignant prostatic disease recurrence should be based on a complete clinical evaluation of the patient, which may also include serial serum PSA determinations.

3 Samples should be obtained before biopsy, prostatectomy or prostatic massage, since manipulation of the prostate gland may lead to elevated PSA levels persisting up to 3 weeks.[17]

4 To evaluate the "high-dose hook" effect characteristic of immunoradiometric assays, samples containing PSA values up to 39,000 ng/mL were assayed by the Coat-A-Count PSA IRMA procedure and found to yield results well above 150 ng/mL, the concentration of the highest calibrator.

5 PSA expression may be altered due to hormonal therapy for prostate cancer. Consequently, a low PSA result following a prostatic cancer treatment which includes hormonal therapy may not adequately reflect the presence of residual or recurrent disease.[23]

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Technical Assistance

For questions regarding the Coat-A-Count PSA IRMA kit or its reagents, or for further advice on technique, data reduction, quality control or expected values, please contact DPC's Technical Services department or your National Distributor.

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